REMARKS

Claims 1-27 are presently under examination. No claims are amended, added or cancelled herein. Claims 28-59 stand withdrawn from consideration as directed to a non-elected invention.

Rejections under 35 U.S.C. § 112, first paragraph

The objection to the specification and corresponding rejection of claims 1-27 under 35 U.S.C. §112, first paragraph, as containing subject matter not described in the specification so as to enable one skilled in the art to practice the claimed invention is respectfully traversed. Applicant respectfully submits that the specification enables the full scope of claims 1-27.

To support the enablement rejection, the Office Action mainly asserts that no working example is provided of any efficacy of "SNP treatment" (current Office Action, Paper No. 803, mailed August 14, 2003, paragraph bridging pages 3 and 4).

Enablement has to be provided for what is claimed as the invention. While the Examiner appears to focus the rejection on the enablement of "SNP treatment" methods, the claims presently being examined are directed to compositions and do not recite any "SNP treatment" methods. In particular, base claim 1 is directed to a composition of compounds effective for treating a pathology, the composition encompassing at least two compounds that modulate the activity of one or more molecules associated with a SNP, wherein each compound modulates the activity of at least one molecule associated with one or more SNPs, and wherein the combination is effective for at least one patient having the pathology. Base claim 20 is directed to a composition of compounds effective for treating a pathology, the composition encompassing at least two compounds that modulate the activity of a single target

protein associated with one or more SNPs, wherein said combination is stably effective for at least one patient having the pathology.

In *Amgen, Inc. v. Hoechst Marion Roussel, Inc*, 232 F.3d 905 (Fed.Cir. 2000), the Federal Circuit clarified the enablement requirement:

> The specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without "undue experimentation."

Id. (citing *Genentech, Inc. v. Novo Nordisk, A/S,* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991))

In *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 47 U.S.P.Q.2d 1705 (Fed. Cir. 1998), the Federal Circuit clearly stated that routine experimentation does not constitute undue experimentation:

> The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

Id. (Emphasis added) (citing *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d at 1564, 37 U.S.P.Q.2d at 1623); see also *In re Wands*, 858 F.2d at 736-40, 8 U.S.P.Q.2d at 1403-07.

In view of the above, it is apparent that enablement has to be provided by the specification for making and using the claimed compositions without undue experimentation. The claims at issue recite a composition of compounds that modulate the activity of one or more target molecules associated with one ore more

SNPs, each compound capable of modulating at least one target molecule associated with one or more SNPs. A component compound of a composition of the invention modulates a target molecule associated with one or more SNPs. The specification teaches that, for a particular pathology, one or more SNPs can be correlated with the symptoms, etiology, side-effects or progression of treatment of that pathology as well as with the efficacy, or toxicity, or both, of a compound used for treating the pathology (specification as filed, page 9, lines 3-9). As further guidance to the skilled person, the specification teaches that patients with a particular pathology have a unique combination of genetic variations correlated with a pathology that can be referred to as the genetic profile or genotype (specification as filed, page 9, lines 20-29).

With regard to identification of a SNP, the specification provides teachings and guidance by disclosing that a SNP can be identified by finding a difference in the nucleotide sequence of an individual compared to the most common nucleotide sequence of the overall population (specification as filed, page 10, lines 17-20). The specification further describes and provides patent citations for methods for SNP identification that are well known in the art, including hybridization stability methods such as SSCP, where the hybrids are identified, for example, by electrophoretic analysis, denaturing HPLC or addressable DNA array hybridization (specification as filed, page 10, lines 17-26). The specification provides additional guidance to the skilled person by disclosing that a perturbation resulting from the hybrid instability can be exploited to detect SNPs by its impact on enzymatic reactions such as restriction endonucleases (RFLP), allele-specific oligonucleotide ligation, allele-specific cleavage, allele-specific PCR, and allele-specific LCR (specification as filed, page 10, line 26, to page 11, line 2). In addition, the specification discloses other methods for detecting SNP genetic variations including use polymerase-dependent primer extension techniques such as GBA which uses single nucleotide extension or

limited extension from a specific primer for analysis by, for example, mass spectrometry (specification as filed, page 11, lines 2-8). The specification further teaches that correlation of data to identify a site of a genetic variation such as a SNP can be carried out by sequence comparison of the results of the taught assays for multiple individuals and provides several citations to the skilled person that provide further guidance on methods for sequence comparison (specification as filed, page 11, lines 8-13). Thus, the specification provides considerable teachings and guidance to the skilled person for detection of SNPs.

With regard to establishing a correlation, the specification teaches that certain genetic variations are correlated with a pathology or treatment of a pathology, for example, the SNP encoding the change from normal hemoglobin to sickle hemoglobin in sickle cell anemia (specification as filed, page 11, lines 13-17). The specification further discloses that methods for using a variety of patient determinants such as genetic variations to establish if one or more determinants are correlated with a pathology, or if one or more determinants are correlated with treatment of a pathology, are known in the art and provides a number of citations to patents and international patent publications that are incorporated by reference for their teachings with regard to establishing such correlations (specification as filed, page 11, lines 17-24).

Applicant further respectfully submits that methods for identifying a target molecule associated with one or more SNPs that plays a role in the symptoms, etiology, complications or treatment of a pathology were known in the art at the time the present application was filed. In this regard, Applicant submits as Exhibits A and B, publications by Hijikata et al., *Intervirology* 43(2):124-127 (2000) and Lambert et al., *J. Med. Genet.* 38(6):353-355(2001), respectively. Hijikata et al. report the identification of a SNP in the MxA gene promoter correlated with the response to hepatitis C patients to interferon treatment. This reference describes the

identification, via routine methods, of a target molecule associated with a SNP that plays a role in the treatment of a pathology. Lambert et al. describe a SNP in the presenilin 1 promoter that is associated with an increased risk of Alzheimer's disease and an increased risk of Abeta protein load in the brain. This reference describes identification, via routine methods, of two target molecules associated with a SNP that play a role in the symptoms of a pathology. Applicant respectfully submits that Exhibits A and B evidence that the identification of a target molecule that is associated with one or more SNPs that plays a role in the symptoms, etiology, complications or treatment of a pathology were known in the art at the time the present Application was filed.

With regard to compounds effective against a target molecule associated with one ore more SNPs, the specification teaches that the compound can modulate the activity of a target molecule that plays a role in the symptoms, etiology, complications or treatment of a pathology as well as can modulate the activity of a target-protein associated with one or more genetic variations that plays a role in the symptoms, etiology, complications or treatment of a pathology (specification as filed, page 7, lines 9-14). The specification further discloses as an example a protease normally having a glutamate at a position near the active site that can have increased proteolytic activity as a result of a single nucleotide polymorphism arising in which the glutamate is changed to alanine, resulting in a particular SNP playing a role in a pathology caused by increased proteolytic activity (specification as filed, page 7, lines 17-24). A compound, such as a protease inhibitor, can be effective against a protease target protease with this SNP by inhibiting the proteolytic activity of the protease. Armed with the guidance provided by the specification, the skilled person would have been able to prepare a composition encompassing at least two compounds, for example protease inhibitors, after confirming via routine methods not requiring undue

experimentation, that each compound modulates the activity of a target molecule, for example a protease, that is associated with one or more SNPs.

In addition to the teachings and guidance provided by the specification with regard to identifying a SNP in a target molecule, identifying a compound that modulates the activity of a target molecule associated with one or more SNPs, and establishing a correlation between a pathology or treatment thereof and a genetic variation, the specification discloses an algorithm for determining the efficacy and/or toxicity of a combination of two or more compounds for a population of patients having a pathology (specification, page 33, line 22, to page 34, line 10). Further with regard to determining efficacies, the specification exemplifies optimization of efficacy for five compounds with additive efficacies for five equally populated as well as for two compounds with additive efficacies for two variably populated genotypes (specification, Examples I and II, pages 36-44). Thus, the specification exemplifies determination and optimization of efficacy for a composition of the invention, teaching the skilled person both how to make and how to use the claimed compositions.

In view of the above, Applicant submits that the specification provides sufficient teachings to enable those in the art to can make and use the invention compositions without "undue experimentation." Accordingly, Applicant respectfully requests withdrawal of the objection to the specification and corresponding rejection of claims 1-27 under 35 U.S.C. §112, first paragraph, as containing subject matter not described in the specification so as to enable one skilled in the art to practice the claimed invention.

Rejection under 35 U.S.C. § 102

Applicant respectfully traverses the rejection of claims 1-27 under 35 U.S.C. § 102(e), as allegedly anticipated by United States Patent No. 6,248,308, to Rubin. For

the reasons that follow, Applicant respectfully submits that United States Patent No. 6,248,308, to Rubin does not describe within its four corners each element of Applicant's claimed invention, either expressly or inherently, and cannot support the present rejection.

Base claim 1 is directed to a composition of compounds effective for treating a pathology, the composition encompassing at least two compounds that modulate the activity of one or more target molecules associated with one or more Single Nucleotide Polymorphisms (SNPs), wherein each compound modulates the activity of at least one target molecule associated with one or more SNPs, and wherein the combination is effective for at least one patient having the pathology. Base claim 20 is directed to a composition of compounds effective for treating a pathology, the composition encompassing at least two compounds that modulate the activity of a single target protein associated with one or more SNPs, wherein said combination is stably effective for at least one patient having the pathology.

> [A]nticipation requires that the four corners of a single, prior art document describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation.

Advanced Display Sys., Inc. v. Kent State Univ., 212 F.3d 1272, 1282 (Fed.Cir. 2000) (citing *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347 (Fed.Cir. 1999)); and *In re Paulsen*, 30 F.3d 1475, 1479 (Fed.Cir. 1994)).

The Office Action, at page 6, first paragraph, alleges that Rubin describes a composition of compounds effective for treating a pathology, where the composition includes at least two compounds that modulate the activity of one ore more target molecules associated with the pathology, wherein the combination is effective for at least one patient having the pathology. The Office Action further alleges that Rubin

inherently teaches that the target molecules are associated with one or more SNPs, wherein each compound modulates the activity of at least one target molecule.

The alleged inherency is based a second reference, United States Patent No. 6,316, 196, to Morten, which is cited for the assertion that "it was known to an ordinary artisan at the time the invention was made that leukotriene mediated disease is *caused by* a SNP, which can be effectively treated with leukotriene inhibitors." According to Applicant's reading of Morten, the patent appears to merely show a correlation, not a causative connection, between leukotriene mediated disease and certain polymorphisms in the LTC_4 synthase gene, which the Office appears to assert is the target molecule according to claim 1 as well as a target protein according to claim 20. The passage cited by the Examiner to show that leukotriene mediated disease is "caused by a SNP" merely describes a method where the leukotriene mediated disease is first diagnosed by establishing the presence of four SNPs in the LTC_4 synthase gene and subsequently treated by administration of a leukotriene inhibitor. Contrary to the Examiner's assertion, there is no indication in the Morten patent that makes it an inherent teaching of Rubin that the target molecules are associated with one or more SNPs, wherein each compound of the composition modulates the activity of at least one target molecule. Consequently, Rubin teaches neither expressly nor inherently that the target molecules are associated with one or more SNPs, wherein each compound of the composition modulates the activity of at least one target molecule.

The Office Action, at page 6, first paragraph, further supports the present rejection by indicating that norastemiozole and a leukotriene inhibitor, represent the two compounds of Applicant's claim 1 and, presumably although not stated, claim 20. Based on that premise, to meet each element of the claim 1 of Applicant's invention, each of the two compounds has to modulate the activity of at least one target molecule associated with one or more Single Nucleotide Polymorphisms

(SNPs). With regard to claim 20, both compounds have to modulate the activity of a single target protein associated with one or more SNPs.

Applicant respectfully submits that neither compound, norastemiozole or leukotriene inhibitor, is shown to modulate the activity of a target molecule, including a target protein, associated with a SNP. There is no description in the Morten patent to indicate leukotriene inhibitors modulate the LTC_4 synthase gene or any other target molecule associated with a SNP. In addition to not meeting the claim 1 element of showing that one of the compounds in the composition, a leukotriene inhibitor, modulates the activity of the LTC_4 synthase gene or any other target molecule, the Examiner also fails to show that the second compound, norastemiozole, modulates the activity of any target molecule associated with a SNP. There is no teaching, expressly or inherently, in the Rubin patent of a composition of compounds effective for treating a pathology, the composition encompassing at least two compounds that modulate the activity of one or more target molecules associated with one or more Single Nucleotide Polymorphisms (SNPs), wherein each compound modulates the activity of at least one target molecule associated with one or more SNPs, and wherein the combination is effective for at least one patient having the pathology. Furthermore, with regard to claim 20, there is no teaching, expressly or inherently, in the Rubin patent of a composition of compounds encompassing at least two compounds that modulate the activity of a single target protein associated with one or more SNPs, and wherein the combination is effective for at least one patient having the pathology.

In view of the above discussion, Applicant submits that the cited reference fails to teach each and every element of the claimed invention, either expressly or inherently, and therefore fails to anticipate the claimed invention. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

CONCLUSION

In light of the Remarks herein, Applicant submits that the claims are now in condition for allowance and respectfully requests a notice to this effect. Should Examiner Chakrabarti have any questions, he is invited to call the undersigned attorney.

Respectfully submitted,

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